REMARKS

Claim amendments

Independent claims 29 and 55 are amended to add the limitation that "the method does not include treatment with a radiolabeled antibody." Those claims, as well as claims 34, 69, and 94, are amended to delete the recitation that the antibody is "unlabeled." Claims 41, 67, and 94 are amended to correct the spelling of "fludarabine." Claim 92 is amended to correct the spelling of "toremifene." Claims 84 and 85 are amended to replace the former trademark, "Oncovin," with the corresponding nonproprietary name, vincristine. Claims 95-98 are added.

The recitation that "the method does not include treatment with a radiolabeled antibody" in claims 29, 55, and 95 is supported, *e.g.*, at paragraph 0140 ("Treatment of hematologic malignancy, such as CLL … according to the invention will comprise the administration of a therapeutically effective amount of an anti-CD20 antibody, … alone or in conjunction with other treatment(s), e.g., … radiotherapy (e.g., whole body irradiation, or treatment with radiolabeled antibodies)"). *See also* paragraphs 0050, 0260, 0280, and the examples.

New claims 96-98 recite that the "radiation is not used in conjunction with the therapeutic anti-CD20 antibody," as supported, *e.g.*, at in paragraph 0280. Independent claims 97 and 98 otherwise track the language of claims 29 and 55, respectively.

Corrections of the spellings of fludarabine and toremifene in claims 41, 67, and 94 rectify obvious errors.

The substitution of vincristine for Oncovin relies on the art-recognized equivalence of the proprietary and nonproprietary names for this drug. *See*, *e.g.*, Smalley *et al.*, *N. Engl. J. Med.* 327: 1336-41 (1992), of record, at 1336, right column. Also, the nonproprietary name, vincristine, appears in the original disclosure at paragraph 0290.

The amendments add no new matter to the disclosure.

Interviews

Applicant thanks the examiner for the personal interviews conduced on 5 October 2006 and 23 April 2007.

The examiner's summary of the interview mailed on 13 October 2006 accurately records the substance of the first interview. Applicant's representative discussed the reply filed on 8 October 2006. Kaminski (US 6,090,365) and Jensen (*Ann. Hematol.*, 1998) were discussed. Applicant's representative provided the examiner a copy of the latter reference.

On 23 April 2007, applicant's representatives met with the examiner to discuss the outstanding rejections. The art rejections based on Kaminski '365 were discussed. The examiner explained the Office's view that the claims could be interpreted to cover the administration of an unlabeled antibody followed by a radiolabeled antibody. Applicant's representatives discussed possible ways to amend the claims to exclude such a possibility. The examiner indicated amending the claims to exclude a step of administering a radiolabeled antibody would address the Office's concerns.

Support for the recitation of "unlabeled" antibodies was also discussed. Applicant pointed out several sections of the specification that draw a distinction between combination protocols and those that rely on a therapeutically active unlabeled antibody, such as rituximab, to achieve a therapeutic effect. Applicant also noted that Example 2, which includes the recitation of "unlabeled" previously identified, falls within a section of the disclosure that is expressly identified as providing support for the methods of the invention. Applicant thus urged that in the context of the disclosure as a whole, support for claims requiring the use of unlabeled antibodies was evident. The examiner agreed to review the specification in this regard.

Objections to the claims

The examiner objected to claims 41, 67, and 89 for inconsistent spellings of "fludarabine" and "toremifine." Claims 41, 67, 92, and 94 have been amended to conform all of the claims to the correct spellings of the names of these agents. Applicant believes that these amendments correct the noted informalities and therefore requests that the examiner withdraw the objections. Applicant has also reviewed the specification and confirms that the correct spellings of these names are used throughout.

35 U.S.C. § 112, first paragraph

The Office rejected all of claims 29-94 under § 112, first paragraph, as allegedly containing new matter with respect to the recitation of "unlabeled." Applicant respectfully traverses this ground of rejection.

The examiner has taken the position that the specific occurrence of the word "unlabeled" occurs only in Example 2, which primarily discusses prior experience with the use of anti-CD20 antibodies to treat non-Hodgkin's lymphoma (NHL). As discussed at the interview of 23 April, however, this discussion is presented to support the disclosure of the invention. For example, paragraph 0300, immediately preceding the examples, states that "[t]he examples are intended to provide clinical evidence in support of the efficacy of the invention." This introductory comment provides evidence that the inventors considered that the use of unlabeled antibodies was specifically within the scope of the invention.

This perspective is supported by the examples. Examples 1, 3, 4, and 5 refer to actual clinical experiments using the RITUXAN drug product, which (by definition) comprises an unlabeled chimeric antibody, rituximab. This antibody is disclosed as having the desirable attributes of the "[u]nlabeled immunoglobulins" described in Example 2. *Compare* the language and content of paragraphs 0330 (unlabeled Mabs) and 0360 (rituximab). Viewed in context, it is clear that rituximab is representative of therapeutic antibodies having the desirable attributes of the unlabeled antibodies described at paragraph 0330.

The disclosure also provides unambiguous support for distinguishing between unlabeled therapeutic antibodies and radiolabeled therapeutic antibodies. For example, paragraph 0050 describes "[p]revious reported therapies" involving the administration of an anti-CD20 antibody "alone or in conjunction with a second radiolabeled anti-CD20 antibody." The concept that the "first" anti-CD20 antibody is not radiolabeled is clearly reflected in this discussion. Similarly, paragraph 0140 provides that the methods of the invention "will comprise the administration of a therapeutically effective anti-CD20 antibody, … alone or in conjunction with other treatments [including] treatment with radiolabeled antibodies."

The term "unlabeled" is deleted from the amended claims to advance prosecution. Also, in view of the added limitations in several claims requiring that "the method does not include

treatment with a radiolabeled antibody" or that "radiation is not used in conjunction with the therapeutic anti-CD20 antibody," the affirmative recitation that the administered antibody is unlabeled would be duplicative. These new limitations distinguish over the prior art for all of the reasons discussed with respect to the recitation of "unlabeled" in applicant's last reply.

35 U.S.C. § 102(e)

The Office has rejected claims 29-32, 42, 44, 46, 53-58, 68, 70-72, 79-88, 90, and 91 under § 102(e) as anticipated by Kaminski '365. Applicant respectfully traverses this ground of rejection.

Applicant reiterates that Kaminski does not anticipate a method of treating CLL for all of the reasons enumerated in the reply filed on 8 October 2006.

First, no specific embodiment involving the treatment of CLL is set forth in the specification, either in the form of an actual example or a prophetic example. As discussed with particularity in the last reply, the only consideration of CLL in the reference is in the context of generic discussions that might be amenable to treatment according to the methods that Kaminski describes. Such a generic contemplation does not constitute a description of specific subject matter meeting all of the limitations of the claims, as is required to establish anticipation under § 102.

Second, Kaminski does not teach or suggest that the unlabeled antibody used according to its protocol is in an amount effective to treat any disease. Instead, as discussed in the previous response, the function of the unlabeled antibody is to enhance the efficacy of the radiolabeled antibody.

The amendments set forth above more explicitly distinguish the claims over the disclosure of Kaminski. Claims 29 and 55 now require that the method does not include treatment with a radiolabeled antibody. This limitation expressly excludes the combination protocols described in the Kaminski patent, and it also precludes the use of a radiolabeled antibody as the anti-CD20 antibody of the recited administration step. The claims retain open transitional language ("comprising") and are thus open to the inclusion of other therapeutic steps, so long as those other therapeutic steps do not include the administration of a radiolabeled antibody.

35 U.S.C. § 103(a)

All of claims 29-94 were rejected under § 103(a) over the combination of Kaminski '365; McLaughlin (*J. Clin. Oncol.*, 1998); Stenbygaard (*Br. Cancer Res. Treatment*, 1993); and Lerner (US 6,399,649). Applicant traverses this ground of rejection.

A comparison of the claimed invention to the prior art must take account of the important fact that CLL is not the same disease as low-grade or follicular NHL. Evidence of record that establishes this fact was discussed in the last Office action. Briefly –

- CLL has different molecular origins and clinical characteristics as compared to other B cell tumors. *See* Cogliatti (*Sw. Med. Weekly*, 2002); Staudt (*Adv. Immunol.*, 2005).

- The density of CD20 molecules on the surface of CLL cells is lower than on NHL cells. *See* Almasri (*Am. J. Hematol.*, 1992) .

- It was recognized in the art that the high density of CD20 on NHL cells is a factor that makes CD20 an especially useful target for antibody therapy. *See* Multani (*JCO*, 1998).

- The inventors recognized and taught that CLL is sufficiently different from NHL that one of ordinary skill would not have been able to extrapolate from experiences using an anti-CD20 antibody to treat NHL to predict whether a similar treatment would be effective for CLL. *See* specification at paragraph 0130.

- Post-filing evidence confirms that these facts would have led one of skill to expect that CLL would be less susceptible to anti-CD20 therapy than would be NHL. *See* Herold (*Ann. Hematol.*, 2000).

In view of these observations, it is apparent why the clinical trial reported in McLaughlin (*JCO*, 1998) *specifically excluded* patients having CLL from the clinical trial of rituximab that it reports. This evidence supports the view that those of ordinary skill considered CLL sufficiently

different in character from NHL that CLL patients should not be included in a trial designed to assess the efficacy of treating NHL patients with rituximab.

Against this backdrop, the fact that Kaminski does not differentiate between CLL and any of the many other B cell tumors it describes is significant. Although it teaches that CLL is one disease that might be treated with a radiolabeled antibody directed against one of the several B cell antigens it discusses, Kaminski provides no teaching to counter the evidence that one of ordinary skill would not have expected CLL to be treatable in the same manner as NHL. Moreover,

Additionally, the Kaminski reference relates to a combination protocol that includes a radiolabeled antibody. Kaminski provides no motivation for one of ordinary skill to modify its teachings to omit the use of a therapeutic radiolabeled anti-CD20 antibody, as claims 29, 55, and the claims that depend from them now require.

Claims 34, 60, and 94 have been amended to delete the requirement that the antibody be unlabeled. Claims 34 and 60 require that the anti-CD20 antibody be administered at a dosage of about 500 to about 1500 mg/m^2. The prior art does not teach or suggest using these dosages for any treatment. As evidenced by the cited McLaughlin reference, a dose of 375 mg/m^2 was known in the art for the treatment of NHL using rituximab. Indeed, when the provisional application to which this application claims priority was filed, 375 mg/m^2 was the FDA-approved dosage for rituximab in the treatment of relapsed or refractory low-grade or follicular, CD20-positive, B cell NHL. None of the cited references teach that it would be desirable to use doses of an anti-CD20 antibody significantly higher than those that were known for treating NHL or any other B cell tumor. The Office has not set forth a *prima facie* case that it would have been obvious to use the higher dosages required by claims 34 and 60.,

Claim 94 specifies the treatment of fludarabine-resistant patients. Neither Kaminski nor any of the other cited references indicates that anti-CD20 immunotherapy would be effective in such a subpopulation of patients. The prior art provides no basis for one of ordinary skill to expect that patients who are refractory to one ordinarily effective treatment would respond to antibody therapy.

McLaughlin, as noted above, specifically excludes CLL patients from the trial it reports. Thus, in view of the recognized clinical heterogeneity of B cell tumors, McLaughlin provides no teachings that pertain to the treatment of CLL.

Stenbygaard is a paper that describes the use of tamoxifen and toremifene to treat breast cancer. While it serves as evidence that these two agents were known, it teaches nothing to one of ordinary skill bearing on a treatment for CLL. The examiner's assertion that McLaughlin provides motivation "to efficaciously treat cancer," stated at page 8 of the last Office action, is no more relevant to the treatment of the *specific* cancer recited in the claims than would be a statement that it motivates one to efficaciously treat "disease" according to the methodology it presents.

Finally, Lerner '649 concerns the use of small-molecule phosphodiesterase inhibitors to treat CLL. It provides no teaching or suggestion that an anti-CD20 antibody would also be useful to treat CLL. Moreover, a person of skill would not have considered a small-molecule phosphodiesterase inhibitor to be analogous to an anti-CD20 antibody. Thus , one of ordinary skill would not have turned to Lerner to predict whether any of the claimed methods would be efficacious.

For the reasons set forth above, the examiner has failed to set forth a *prima facie* case of obviousness. Applicant requests reconsideration of the rejection.

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Conclusion

Applicant believes that this reply fully responds to the grounds of objection and rejection raised in the last Office action and respectfully requests that they be withdrawn.

The examiner is invited to contact the undersigned attorney should she have any questions concerning the application.

Respectfully submitted,

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